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(54) COMPOSITION CONTENANT DU POLYACRYLATE, DU POLYTERPENE, DE LA NITROGLYCERINE ET EVENTUELLEMENT DU POLYVINYLE ACETATE

(54) COMPOSITION CONTAINING POLYACRYLATE, POLYTERPENE, NITROGLYCERINE AND POSSIBLY POLYVINYL ACETATE

(57) L'invention concerne une composition s'appliquant sur la peau et contenant a) un copolymère d'acrylate renfermant 25-40 % en poids de méthylacrylate, 50-70 % en poids de 2-éthylhexylacrylate, 1-10 % en poids d'acide acrylique, b) un polyterpène et c) de la nitroglycérine. Cette composition sert à la prophylaxie ou au traitement de la cardiopathie coronarienne.

(57) The invention relates to a composition applied to the skin and containing a) an acrylate copolymer containing between 25 and 40 weight % methylacrylate, between 50 and 70 weight % 2-ethylhexylacrylate and between 1 and 10 weight % acrylic acid; b) a polyterpene; and c) nitroglycerine. Said composition is used for the prophylaxis or treatment of coronary heart disease.

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(54) Title: COMPOSITION CONTAINING POLYACRYLATE, POLYTERPENE, NITROGLYCERINE AND POSSIBLY POLYVINYL ACETATE

(54) Bezeichnung: ZUSAMMENSETZUNG, ENTHALTEND POLYACRYLAT, POLYTERPEN, NITROGLYCERIN UND WAHLWEISE POLYVINYLACETAT

(57) Abstract

The invention relates to a composition applied to the skin and containing a) an acrylate copolymer containing between 25 and 40 weight % methylacrylate, between 50 and 70 weight % 2-ethylhexylacrylate and between 1 and 10 weight % acrylic acid; b) a polyterpene; and c) nitroglycerine. Said composition is used for the prophylaxis or treatment of coronary heart disease.

(57) Zusammenfassung

Eine Zusammensetzung zur Applikation auf der Haut, die enthält: a) ein Acrylat-Copolymer, enthaltend 25-40 Gew.-% Methylacrylat, 50-70 Gew.-% 2-Ethylhexylacrylat, 1-10 Gew.-% Acrylsäure, b) ein Polyterpen, c) Nitroglycerin, dient zur Prophylaxe oder Behandlung der koronaren Herzkrankheit.

The invention relates to a composition for applying nitroglycerine to the skin. Using this composition, a continuous and metered release of the active substance to the skin is achieved, the composition acting as an active substance depot. The composition comprises: an acrylate copolymer containing 25-40% by weight methyl acrylate, 50-70% by weight 2-ethylhexyl acrylate, 1-10% by weight acrylic acid; a polyterpene based on alpha-pinene or beta-pinene; and at least nitroglycerine as active substance. The melting point of the polyterpene is situated within the range from 37°C to 140°C; its fraction is not greater than 30% by weight, based on the dry weight of the composition. The composition is used preferably for prophylaxis or treatment of coronary heart disease, especially of angina pectoris.

Customary therapeutic active substances for prophylaxis or treatment of coronary heart disease are esters of nitric acid. Preferably nitroglycerine is used. Nitroglycerine leads to peripheral vasodilation and thereby brings about a reduction in the cardial preload and afterload. As a result of this reduction and of the reduction in cardiac work which it causes, there is a fall in the oxygen demand of the heart. Furthermore, nitroglycerine brings about a reduction in the extravasal component of coronary resistance and so leads to an improvement in the supply of oxygen.

Acute attacks of angina pectoris may be treated rapidly and effectively by the sublingual administration of nitroglycerine. This mode of administration leads rapidly to a high active substance plasma level.

Since the plasma half-life of nitroglycerine is only 1-3 minutes, the plasma concentration flattens out again very rapidly. Consequently, sublingual administration is not appropriate for the prophylaxis of attack. Transdermal administration is more suited to this purpose. The systemic absorption rate of nitroglycerine through the skin is approximately 20 $\mu g/cm^2/h$ depending on the site of administration. An advantage in this case is that the bioavailability is not seriously reduced by metabolic processes, owing to circumvention of the first-pass effect in the liver. A priori, only the horny layer of the skin and the size of the administration area are determining factors for the amount of active substance in circulation in the blood. A relatively constant steady-state plasma concentration is obtained over a relatively long period. The transdermal administration of nitroglycerine is therefore the means of choice for effective angina pectoris prophylaxis.

Numerous preparations for the dermal administration of nitroglycerine are presently known. Patch-type systems are predominant. Nitroglycerine is present either in solution or adsorbed on an auxiliary. Known systems include simple matrix systems (US 4,751,087), reservoir systems of complex construction (US 4,725,272), and systems which contain the active substance in a kind of microcapsule (US 3,742,951; US 4,336,243).

For successful therapy it is important that the active substance is released from the preparation to an appropriate extent and subsequently permeates the skin. Whereas the release characteristic of the preparation is determined by the auxiliaries employed, the transdermal absorption of active substance is determined critically by the horny layer of the skin. The absorption may be

increased by the use of penetration enhancers. For instance, US 5,262,165 describes the use of N-methyl-2-pyrrolidone and oleic acid to increase nitroglycerine absorption.

Synthetic acrylate polymers are often used as a preparation base, owing to their nonallergenic nature. A disadvantage is that polyacrylates are very effective solvents for nitroglycerine. This high solubility is synonymous with low thermodynamic activity. As a result, nitroglycerine must be incorporated in a high concentration in order to obtain the required release of active substance.
EP 0 622 075 A1 describes a preparation containing nitroglycerine in a concentration of 50-65% by weight. The disadvantage of such high levels of nitroglycerine lies in its properties. Nitroglycerine reacts to thermal and mechanical stress by explosion, or unwanted changes arise in the properties of the adhesive (reduction in adhesion, and excess softness). In order to obtain preparations with acceptable properties of the adhesive, it is possible to modify the thermodynamic activity, as in US 5,474,783, by including a polysiloxane. Polysiloxanes have low solubility for nitroglycerine, thereby lowering the overall solubility in the preparation. The reduced saturation solubility is reflected in an increased rate of release. By varying the amount of polysiloxane included it is possible within certain bounds to control the release kinetics.

The objective of the present invention is to produce a preparation comprising nitroglycerine. As the base material, the fairly nonallergenic acrylate polymers are used. The preparation is intended to have high thermodynamic activity, thereby securing a high rate of release coupled with the use of low levels of active substance. A high thermodynamic activity may be achieved by

reducing the saturation solubility of the corresponding active substance. This can be realized on the one hand by adding to the preparation an auxiliary which influences the active substance solubility, or by using a base material itself possessing a low active substance solubility.

The base material used is a polyacrylate containing 25-40% by weight methyl acrylate, 50-70% by weight 2-ethylhexyl acrylate, 1-10% by weight acrylic acid. Furthermore, it is important that the vinyl acetate fraction is less than 5% by weight, since vinyl acetate leads to a reduction in the rate of release as the concentration increases (Figures 1 and 2). It must be borne in mind here that vinyl acetate may be present as a copolymer with the acrylate or as a homopolymer.

In order to adjust the nitroglycerine solubility and to improve the consistency, a polyterpene based on alpha-pinene or beta-pinene is added to the composition. Polyterpenes are either naturally occurring substances which on the basis of their biogenesis conform generally to the isoprene rule, comprising $(C_{10})_n$ units, or/are synthetic hydrocarbon resins (terpene resins) which may be prepared by polymerizing monoterpenes. The melting point of the polyterpene is situated within the range from 37°C to 140°C. Examples thereof are Dercolyte A40, Dercolyte S40, Dercolyte A85, Dercolyte S85, Dercolyte A100, Dercolyte S100, Dercolyte A115, Dercolyte S115, Dercolyte A125, Dercolyte S125, Dercolyte A135 and Dercolyte S135.

The influence of the polyterpenes on the rate of release is shown in Figure 3. From this it may be concluded that polyterpenes are able to increase the thermodynamic activity of nitroglycerine.

The preparation may further comprise: metal compounds (aluminum, titanium, and further metal compounds known to the skilled worker); plasticizers (paraffins, cyclic hydrocarbons, vegetable oils, and further plasticizers known to the skilled worker); penetration enhancers (surface-active substances, lipophilic solvents, hydrophilic solvents); tackifiers (rosins, hydrocarbons and other tackifiers known to the skilled worker); active-substance-impermeable backing and/or protective films (polyester, polypropylene, polyethylene and other materials known to the skilled worker).

EXAMPLE:

In the text below, the invention is illustrated on the basis of examples:

EXAMPLE 1 - Formulation using a poly-alpha-pinene

220 g of self-adhesive, carboxyl-containing polyacrylate (Durotak 387-2353, 37.7% by weight in ethyl acetate/hexane mixture), 40 g of poly-alpha-pinene (Dercolyte A85, 70% by weight in petroleum spirit), 20 g of isopropyl palmitate, 20 g of 1,2-propanediol, 100 g of nitroglycerine (22.1% by weight in ethyl acetate), 30 g of acetylacetone and 1 g of aluminum acetylacetonate (4% by weight in ethyl acetate) are mixed and applied as a 300 µm thick film using a coating bar to a siliconized polyester film (Hostaphan RN 100). The film is dried at 40°C for 30 minutes and then laminated with a polyester film (Hostaphan RN 15).

EXAMPLE 2 - Formulation using a poly-beta-pinene

220 g of self-adhesive, carboxyl-containing polyacrylate (Durotak 387-2353, 37.7% by weight in ethyl acetate/hexane mixture), 40 g of poly-beta-pinene (Dercolyte S85, 70% by

weight in petroleum spirit), 20 g of isopropyl palmitate, 20 g of 1,2-propanediol, 100 g of nitroglycerine (22.1% by weight in ethyl acetate), 30 g of acetylacetone and 1 g of aluminum acetylacetonate (4% by weight in ethyl acetate) are mixed and applied as a 300 µm thick film using a coating bar to a siliconized polyester film (Hostaphan RN 100). The film is dried at 40°C for 30 minutes and then laminated with a polyester film (Hostaphan RN 15).

WHAT IS CLAIMED IS:

1. A composition for application to the skin, comprising
   a) an acrylate copolymer containing 25-40% by weight methyl acrylate, 50-70% by weight 2-ethylhexyl acrylate, 1-10% by weight acrylic acid,
   b) a polyterpene,
   c) nitroglycerine.

2. The composition as claimed in claim 1, having a vinyl acetate fraction of less than 5% by weight.

3. The composition as claimed in claim 1 or 2, wherein the melting point of the polyterpene is situated within the range from 37°C to 140°C.

4. The composition as claimed in any of the preceding claims, wherein a polyterpene based on alpha-pinene is used

5. The composition as claimed in any of the preceding claims, wherein a polyterpene based on beta-pinene is used

6. The composition as claimed in any of the preceding claims, wherein the fraction of the polyterpene as a proportion of the dry weight of the preparation is not greater than 30% by weight.

7. The composition as claimed in any of the preceding claims, wherein the fraction of the nitroglycerine as a proportion of the dry weight of the preparation is greater than 20% by weight.

8. A process for preparing the composition as claimed in any of the preceding claims, comprising the steps of initially taking an acrylate copolymer containing 25-40% by

weight methyl acrylate, 50-70% by weight 2-ethylhexyl acrylate, 1-10% by weight acrylic acid and adding a polyterpene and an active substance.

9. The use of a composition as claimed in any of the preceding claims for prophylaxis or treatment of coronary heart disease, especially of angina pectoris.

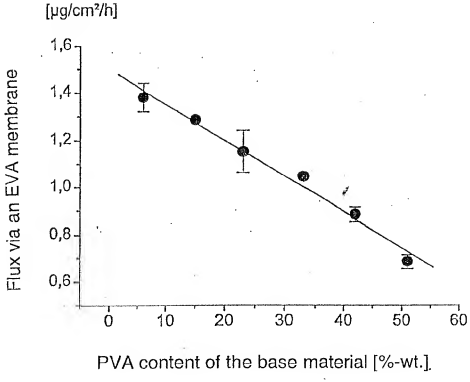
[µg/cm²/h]
1,6
1,4
1,2
1,0
0,8
0,6
Flux via an EVA membrane
0
10
20
30
40
50
60
PVA content of the base material [%-wt.]

FIGURE 1

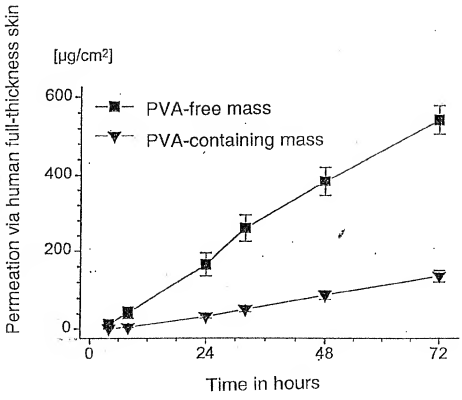
Permeation via human full-thickness skin
[µg/cm²]
600
400
200
0
PVA-free mass
PVA-containing mass
0
24
48
72
Time in hours

FIGURE 2

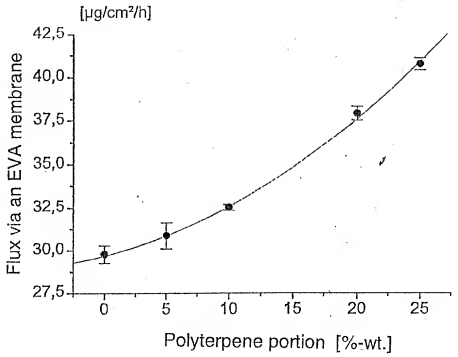
[µg/cm²/h]
42,5
40,0
37,5
35,0
32,5
30,0
27,5
Flux via an EVA membrane
0
5
10
15
20
25
Polyterpene portion [%-wt.]

FIGURE 3